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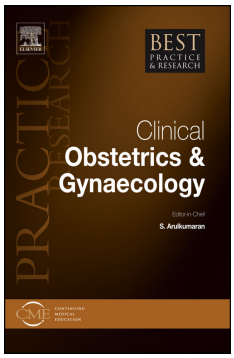


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**TITLE PAGE**

# Staging for endometrial cancer: the controversy around lymphadenectomy– can this be resolved?

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**Abstract**

Endometrial cancer remains the most common malignancy of the female genital tract. Lymph node metastasis is one of the most important prognostic factors and stratification into pelvic lymph node invasion (stage IIIC1) and para-aortic lymph node invasion (stage IIIC2) improved the predictive value of the 2009 FIGO classification.

Radiological examination such as magnetic resonance imaging and positron emission tomography–computed tomography do not have good enough sensitivity to avoid lymphadenectomy for the assessment of lymph node invasion. Prediction scores are becoming more and more valuable to exclude lymph node metastasis in low risk groups and biomarkers could help to identify patients with high risk lymph node metastatic probability.

The therapeutic role of lymph node dissection remains debated. Several endpoints can be considered to evaluate the opportunity of lymphadenectomy in endometrial cancer.

Firstly, we compare survival according to the realization, the extent and the numbers of nodes removed during lymphadenectomy. Secondly, we assess the opportunity of lymphadenectomy in order to tailor adjuvant treatment modalities. Thirdly, we analyze the surgical complication rate after pelvic lymphadenectomy.

**KEY WORDS:** Endometrial cancer; Lymph node metastasis; Prognosis; Staging; Lymphadenectomy; Survival; Prediction; Complications.

## INTRODUCTION

In Europe, EC (Endometrial Cancer) remains the third cancer diagnosed in 2012[1]. Most cases occur in post-menopausal women. Based on histopathology ECs are divided into two categories. Type I are typically low-grade adenocarcinomas that are usually estrogen related, are diagnosed early and have a favorable prognosis. Type II ECs are not hormone dependent and are usually high grade endometrioid adenocarcinomas, papillary serous and clear cell carcinomas and carcinosarcomas[2].

Distant organ metastasis is the most important factor in determining patient survival in cancer. Metastasis is thought to occur through the blood vascular and lymphatic systems. Cancer cells are able to express growth factors and consequently have the capacity to create conduits for tumour metastasis. In EC, pelvic LNs (Lymph Nodes) are the most frequent location of metastasis. The major lymphatic trunks are the utero-ovarian (infundibulopelvic), parametrial, and presacral, which drain into the hypogastric, external iliac, common iliac, presacral, and para-aortic nodes[3]. Although a direct route of lymphatic spread from the corpus uteri to the para-aortic through the infundibulopelvic ligament has been suggested from anatomical and sentinel LN studies[4], direct metastases to the para-aortic LN is uncommon. This reflects how lymphatic drainage patterns of the uterus are complex, particularly when compared to those observed in mapping studies of cutaneous or breast malignancies. At a larger scale, the underlying controversy around the clinical benefit of lymphadenectomy has not been solved. Here, we aim to summarize the main findings related to this commonly performed surgical staging procedure.

## PROGNOSTIC VALUE OF LYMPH NODE METASTASIS

LN metastasis constitutes one of the most important prognostic factors of EC. Since 1988 this information is included in the International Federation of Gynecology and Obstetrics (FIGO) classification. In 2009, the FIGO revised the classification of EC. Apart from merging FIGO 1988 stages IA and IB, LN invasion has been stratified into pelvic LN invasion (stage IIIC1) and para-aortic LN invasion (stage IIIC2). The prognostic performances of the 1988 and 2009 FIGO staging systems have been compared using the concordance indexes. The FIGO staging systems were not significantly different[5, 6]. Others studies however have suggested that the 2009 FIGO staging system for EC is highly prognostic[7, 8], particularly because stages IIIC1 and IIIC2 have different prognosis (five year overall survivals are 57% and 49% respectively[7])

### An independent prognostic factor?

Primary pathological characteristics (myometrial invasion, cervical stromal invasion, histological type, lymphovascular space invasion (LVSI) and grade) are associated with the occurrence of LN metastasis. Consequently, we cannot exclude that uterine risk factors associated with LN metastasis may negatively impact survival independently of LN involvement[9-11]. To answer this question, Barrena Medel et al. compared the prognostic significance of uterine risk factor and nodal metastases and determined the independent effects on outcome[12]. Their results suggest that LN metastasis is an independent and the major prognostic factor since survival in patients with LN metastasis and without uterine risk factors was worse when compared with patients without LN metastasis and with uterine risk factors.

Another approach in order to determine the prognostic impact of LN metastasis consists in building a score to predict survival in EC and in analyzing the impact of lymphadenectomy on

the accuracy of this score. Such a score has been developed by Abu Rustum et al.[13] and validated externally[14]. This score was designed to predict three year survival probability and comprised LN status. More precisely, the number of negative LNs was taken into account in this score as well as 1988 FIGO stage, age at diagnosis, final FIGO grade and histologic subtype. In this score, LN status was considered for LN metastatic risk assessment since FIGO classification was one of the nomogram component and consequently LN positive cases were assigned stage IIIC. Base on their preliminary findings showing that patients who had more regional LNs examined were likely to be more accurately assigned to the correct FIGO stage and because adding positive LNs in the multivariate model did not increase the score's predictive accuracy, the authors decided to include the number of negative LNs into the multivariate model. This characteristic remained significantly associated with survival.

**Lymph Node ratio**

LN ratio is defined as the number of metastatic LNs to the total number of removed LNs. This parameter incorporates not only the burden of nodal disease and cancer spread but also the extent and quality of surgical staging. Polterauer et al. reported on patients with LN ratios 10% or less, more than 10–50%, and more than 50% had 5-year overall survival rates of 79%, 61%, and 36%, respectively (P<.001). In multivariable analysis, only LN ratio was associated with both progression-free survival and overall survival.

## LOCATIONS OF LYMPH NODE METASTASIS

The incidence of metastases to the pelvic LNs in patients with corpus-confined EC who undergo lymphadenectomy varies between 5% and 18%[15-18]. Para aortic LN metastases are observed between 3 to 11% of patients with EC depending on primary tumoral characteristics. 29 to 67% of patients with pelvic LN metastasis have para aortic involvement[15, 19-25]. At the contrary, only a few percent of patients with negative pelvic LN have para-aortic invasion[22]. Although a direct route of lymphatic spread from the corpus uteri to the para-aortic through the infundibulopelvic ligament has been suggested from anatomical studies[4], direct metastases to the para-aortic LN is uncommon, ranging from 0 to 6% [20, 21, 24, 26-30].

Mariani *et al.* have evaluated LN metastatic risk with distinction between the pelvic and para aortic areas[31]. In their prospective study, pelvic and para aortic lymphadenectomies were systematically performed in 310 patients with EC (exclusion criteria were: grade 1 or 2 endometrioid type with myometrial invasion $\leq$50% and primary tumor diameter $\leq$2 cm). Among those patients, 57 patients (22%) had LN invasion and this concerned the pelvic area in 19 cases (33%), the para aortic area alone in 9 cases (16%) and in both the pelvic and the para aortic areas in 29 cases (51%). Because of the low number of patients with metastatic LN in this study (and in patients with EC more generally) the results of this study should be interpreted with caution.

Odagiri et al. recently focused on the precise mapping of LN metastasis sites in EC[30]. Among the 42 patients with positive LN metastasis, 16 cases (38%) in the pelvic area alone, 7 cases (16 %) in the para aortic area alone, and 19 cases (45 %) in both the pelvic and para aortic areas. One third of positive para aortic LN were above the inferior mesenteric artery (IMA) without positive LN below IMA. Metastasis to the deep inguinal nodes was found to be extremely rare (0.4 %).

Consequently, for an optimal surgical staging, resection of deep inguinal nodes is not recommended, whereas para-aortic lymphadenectomy should be extended up to the level of renal veins. Moreover, because metastasis to circumflex iliac nodes distal to external iliac nodes (CINDEIN) is extremely rare in patients with positive LN[32, 33], those nodes should not be systematically removed.

## PRE OPERATIVE IDENTIFICATION OF LYMPH NODE METASTASIS

Pelvic and para aortic LN dissection is the recommended method for LN staging in EC. However, the probability of LN involvement is low and considering the invasive nature of lymphadenectomy, avoidance of unnecessary lymphadenectomy is mandatory.

### Magnetic Resonance Imaging (MRI)

Few studies report the accuracy of MRI for predicting LN metastasis. The major limitation is using size criteria alone as thresholds for identifying metastatic LNs based on enlargement (usually 10 mm). This size criterion was used in three out of the four studies that showed similar diagnostic accuracy for MRI and sentinel-node biopsy in women with EC in the meta-analysis published by Selman et al.[34]. This meta-analysis included 18 studies and 693 women. A limitation with this meta-analysis is that the included studies did not use diffusion-weighted imaging. LN specific magnetic resonance contrast agents which have been developed to improve LN staging of pelvic cancers. Sensitivity has been reported between 17 and 66%. Specificity appears to be better (73-99%) and since LN metastasis is quite a rare event in EC, NPV is excellent (95-98%).

### Computed Tomography (CT) scan

Few studies have evaluated the accuracy of CT scan for predicting LN metastasis in EC. Accuracy for LN metastasis ranges from 67 to 88%, with a good NPV (81-94%) but poor sensibility and PPV (57% and 31-50% respectively)[38, 39].

**Positron emission tomography/computed tomography (PET/CT)**

PET/CT using fluorine 18 fluorodeoxyglucose (18F-FDG) has been used for staging with different results. The results of a recent meta-analysis including 16 studies[35], pooled diagnostic indices for LN staging were calculated. LN status based on pathology was compared to the results of the PET/CT. Unfortunately, the type of metastasis (micro or macro metastases) was not reported. We presume that only macrometastasis were considered in the studies included in this meta-analysis since the detection and the diagnosis of micrometastasis is not performed in routine practice. Results from this meta-analysis are shown in Table 1. Only patient basis data are presented.

**<insert Table 1 near here>**

The pooled sensitivity of 18F-FDG for detection of LN involvement was low, which reduces its interest in LN staging of EC. However, the specificity was much better. In other words, result of positive 18F-FDG PET in the LN is reliable. Considering pelvic and para-aortic LNs separately, accuracy of 18F-FDG PET was higher for para-aortic LN staging when compared with the pelvic region.

PET/CT has been reported to be more useful than PET alone, its CT component yielding helpful anatomical and morphological information. However, subgroup analyses regarding PET versus PET/CT instruments showed higher sensitivity and lower specificity for PET compared with PET/CT studies. These differences were not statistically different between PET and PET/CT studies ($P = 0.3$ for sensitivity and $P = 0.8$ for specificity)[35].

Altogether, sensitivity of 18F-FDG PET imaging is not good enough to justify its routine use for preoperative LN staging in EC. On the other hand, specificity of 18F-FDG PET imaging is adequate. Further studies with large sample size as well as consistently applied pelvic and para-aortic lymphadenectomy are definitely needed to be able to draw any more specific conclusion.

Recently, fused PET/MRI images of EC have been compared with 18F-FDG contrast-enhanced PET/CT and MRI for the prediction of LN metastasis[36]. Despite patient-based sensitivity, specificity and accuracy for detecting pelvic nodal metastasis of 100%, 96% and 97% for both fused PET/MRI, the low number of patients included (30 cases), makes it non recommendable systematic radiological examination for the management of patients with EC.

**PREDICITNG LYMPH NODE METASTASIS**

Primary tumoral characteristics, demographical characteristics and CA125 level are associated with LN metastasis in EC. The strongest association is observed with primary tumoral characteristics that include: local extension (myometrial and stroma cervical invasion), subtype, grade, diameter and LVSI. Most of those characteristics are assessable pre operatively (local extension, subtype, grade, diameter) while LVSI status is not. In particular, many studies reported on the accuracy of MRI for the evaluation of the locoregional extension of EC. A systematic review that included 11 studies and 548 women reported that on the detection of deep myometrial invasion[37]. The analysis concluded that contrast-enhanced MRI has a good diagnostic performance in assessing myometrial invasion of EC and is superior to T2-weighted imaging alone. For assessing deep myometrial involvement, its negative predictive value appears relative high and negative findings strongly suggest an absence of deep myometrial involvement However, both contrast-enhanced and T2-weighted have suboptimal positive predictive value. New imaging sequences, such as diffusion-weighted imaging, were only recently introduced and have not been evaluated enough yet. Ultrasound has similar performances for predicting myometrial invasion with accuracy between 67 and 84%[38-41]. Concerning the prediction of stroma cervical invasion, results of MRI are more heterogeneous and less satisfying: accuracy between 46-92%, poor sensitivity and poor positive predictive value. Few studies have evaluated the accuracy of CT scan for the evaluation of the locoregional extension of EC. Accuracy of CT scan for assessment of the outer half of the myometrium ranges between 62 and 87% and very uneven sensibility and specificity reported (10-83% and 42-100% respectively)[42-44]. Concerning cervical stromal invasion, performances of CT scan is insufficient, with low sensibility and PPV (20-25% et 9-14% respectively)[36, 38].

## Scores to predict LN metastasis

Several authors have proposed different scores in order to predict LN metastasis[45-53] (table 2). Most of these use primary tumoral extension (myometrial invasion particularly) and a cut-point was chosen to maximize the negative predictive value and minimize the risk of mislabeling patients with nodal involvement. For all scores, this strategy permits to identify a low risk group of patients accounting for approximately half of patients in whom LN metastatic probability is extremely low (3% or less). Unfortunately, most of these scores have not been validated externally which reduces their generalizability. Similarly, some of those scores are based on definitive pathological results and are only applicable once hysterectomy has been performed.

**<insert Table 2 near here>**

## Groups risk based on LN metastatic probability

In 2000, Mariani et al. proposed an algorithm based on readily ascertainable intraoperative pathologic indicators that would discriminate a subgroup of early EC that would not require lymphadenectomy or adjuvant radiotherapy[54]. 328 patients with endometrioid EC, grade 1 or 2 tumor, myometrial invasion ≤50%, and no intraoperative evidence of macroscopic extrauterine spread were treated surgically. Pelvic lymphadenectomy was performed in 187 cases (57%), and nodes were positive in nine cases (5%). Primary tumor diameter and lymphatic or vascular invasion significantly affected longevity. No patient with tumor diameter ≤2 cm had positive LNs or died of disease. Convery et al. have validated the Mayo algorithm in a multi-center retrospective chart review[55]. Of 110 patients satisfying the Mayo algorithm with an adequate lymphadenectomy, 2% were diagnosed with LN metastasis and

4% subsequently developed recurrent disease. The Mayo algorithm identified with a 98% negative predictive value women who would not benefit from a lymphadenectomy. There was no significant difference in recurrence rate between women who underwent lymphadenectomy and those who did not when the Mayo algorithm was satisfied. Although a small number of patients with advanced stage disease may be missed when applying the Mayo criteria, there is no apparent survival benefit to lymphadenectomy for patients satisfying this algorithm, and these data support its use at other institutions.

In 2013, the ESMO (European Society for Medical Oncology) separated ECs into three risk groups[56]:

- Low risk: Stage IA, grade 1 or 2
- Intermediate risk: Stage IA, grade 3 and Stage IB, grade 1 or 2
- High risk: Stage IB, grade 3 or Type 2

Because of low risk LN metastatic probability, the ESMO does not recommend lymphadenectomy practice in the low risk group. For the intermediate and high risk groups, no recommendation is made by the ESMO.

**Groups risk based on biomarkers to predict LN metastatic probability**

Other approaches have been conducted to try to estimate LN metastatic risk[57]. For example, double negative hormone receptor status in EC curettage has recently been suggested to independently predict LN metastasis[57]. In Trovik et al. study, 26% of patients with combined loss of estrogen-and progesterone receptors expression had LN metastasis. Similarly, stathmin immunohistochemical staining seems to be able to identify EC with LN metastases[58]. The

value, as a predictive marker for response to PI3Kinase inhibition and as a tool to stratify patients for LN sampling remains to be determined. Unfortunately, the impact of lymphadenectomy in terms of survival has not been compared in high risk groups based on such biomarkers. Due to the relatively low frequency of LN metastasis and recurrence in low-risk groups, adequately powered randomized surgical trials have been difficult to conduct. Improved tools (such as biomarkers) identifying patients with high risk for LN metastasis could reduce the required sample size of a randomized clinical trial assessing survival impact of lymphadenectomy.

A part from those biomarkers, LVSI, which is thought to be the beginnings of lymphatic and hematologic metastases has been evaluated in several studies. The interobserver variability in the evaluation of lymphatic and blood vessel invasion cannot be neglected because of the difficulties in recognizing lymphatic channels and blood vessels using standard hematoxylin and eosin staining alone[59]. This could explain why reported rates of LVSI in EC are particularly variable (from 14% to 20% in stage I tumors and between 4% to 37% for all EC stages)[60]. Even in prospective studies, LVSI determination is not systematically performed by pathologists. In such cases, two possibilities are raised: the pathologist did not mention the presence or absence of LVSI because he did not observe any LVSI or because there was no LVSI. Previous studies evaluating LVSI have shown mixed results concerning the impact of LVSI on reccurence rate [61-64]. Despite those contradictory results, distinction by LVSI status has recently been suggested to be more relevant than the distinction between stages IA and IB for predicting survival in stage I EC[65].

Concerning the impact of LVSI on LN metastasis, the association has been suggested in numerous studies[66-68] and LVSI should be considered to be an independent risk factor for LN metastasis. Interestingly, in a multicenter study, the risk for LN metastasis is similar when the LVSI is negative or is not detailed in the pathological report[68].

Unfortunately, LVSI status is only available once hysterectomy is performed. Because the presence of LVSI increases to a large extent, the decision to perform lymphadenectomy because of the presence of LVSI on the hysterectomy specimen, make sense in the perspective to remove LN metastasis.

## SURVIVAL IMPACT OF LYMPHADENECTOMY

In contrast to the prognostic significance of lymphadenectomy, its therapeutic value remains debated. Consequently, there is a high variation in surgical approach worldwide. The following approaches are used, including 1/ omitting lymphadenectomy in patients with presumed early-stage EC, 2/ performing lymphadenectomy only in patients who are at intermediate or high risk for nodal metastases and 3/ performing a complete lymphadenectomy in all EC irrespective of grade and depth of myometrial invasion.

The main reason to perform lymphadenectomy is improvement of survival. Retrospective studies have suggested that complete lymphadenectomy may be associated with improved survival outcomes, particularly for patients with LN metastases[69-72]. In their retrospective series comparing the outcome of 509 patients with presumed early stage according to the number of LNs removed during lymphadenectomy, Cragun et al. have found that patients with poorly differentiated cancers having more than 11 pelvic nodes removed had improved overall survival and progression-free survival compared with patients having poorly differentiated cancers with 11 or fewer nodes removed[16].

Chan et al. based their analysis on the SEER database and consequently evaluated the survival impact of lymphadenectomy on the largest sample of patients with presumed early stage EC[73]. In this study, lymphadenectomy did not improve survival in patients with low risk. At the contrary, in other stages (Stage IB, Grade 3; Stage IC and II-IV), an extensive LN resection was associated with improved 5-year disease-specific survivals.

Two randomized clinical trials showed that lymphadenectomy did not show an overall or recurrence free survival benefit in the early stages of disease. These trials have been criticized for the following reasons: a limited effort with respect to the extent of dissection and LN evaluation, too many low-risk patients, and no direct decision on adjuvant therapy based on

lymphadenectomy result. In particular, ASTEC study has suggested that that there is no benefit from either pelvic lymphadenectomy or postoperative pelvic radiation[17]. Concerning the other randomized study, the Italian trial also showed no improvement in survival for women after pelvic lymphadenectomy, although there was a marginal decrease in the use of postoperative adjuvant radiation therapy after a staging procedure[18].

Because pelvic lymphadenectomy was not proven to have any therapeutic benefit for EC, the SEPAL study » (Survival Effect of Para-Aortic Lymphadenectomy in endometrial cancer) was conducted to establish whether complete, systematic lymphadenectomy, including the para-aortic LNs, should be part of surgical therapy for patients at intermediate and high risk of recurrence[74]. In this retrospective study, both overall and cancer related survival were significantly longer in the pelvic and para-aortic lymphadenectomy group than in the pelvic lymphadenectomy group. This association was also recorded in patients at intermediate or high risk, but overall survival was not related to lymphadenectomy type in low-risk patients. Multivariate analysis of prognostic factors showed that in patients with intermediate or high risk of recurrence, pelvic and para-aortic lymphadenectomy reduced the risk of death compared with pelvic lymphadenectomy. Analysis of patients with intermediate or high risk who were treated with adjuvant radiotherapy or chemotherapy showed that patient survival improved with pelvic and para-aortic lymphadenectomy and with adjuvant chemotherapy independently of one another. In this study, all EC subtypes and stages were included both most tumors were presumed to be limited to the corpus uteri. Importantly, tumoral characteristics were similar between the two groups. However, the main concern about the SEPAL study is that concerning adjuvant therapy, the two groups were not comparable. In patients who underwent both pelvic and para-aortic lymphadenectomy, 77% received chemotherapy whereas this was given in 45% of patients who underwent pelvic

lymphadenectomy alone. Finally, if this study suggests the benefit of both pelvic and para-aortic lymphadenectomy is beneficial in comparison with patients who will undergo pelvic lymphadenectomy alone, it does not imply that extensive lymphadenectomy improves survival in comparison with no lymphadenectomy since abstention for lymphadenectomy was not reported in the SEPAL study.

Taken together, the benefit of lymphadenectomy is less important than we once believed. Nevertheless, lymphadenectomy may help to select patients who need adjuvant therapy (see below).

## COMPLICATIONS OF LYMPHADENECTOMY

If lymphadenectomy was not associated with increased surgical morbidity, it is probable that its practice would not be such a matter of debate. Unfortunately, it is difficult to assess complication rate associated to lymphadenectomy for numerous reasons.

First, in most studies complications rate is only a secondary objective[33, 67, 68]. Second, in many it is often difficult to distinguish complications related to the hysterectomy and those related to the lymphadenectomy. Third, the administration of adjuvant radiotherapy should be taken into account for the interpretation of lymphadenectomy related complication. Similarly, because patients EC often have comorbidities such as diabetes, high blood pressure or obesity, analysis for the occurrence of lymphadenectomy complication should be interpreted with caution.

Because of all those limitations, reported complication rates after lymphadenectomy are particularly variable from one study to another[75, 76]. In patients without adjuvant radiotherapy, reported rates vary between 6 to 25 %[75, 77-79]. Contradictory results have been published concerning the impact of lymphadenectomy on overall complication rate[17, 18, 79]. However, the two randomized studies concerning the impact of lymphadenectomy both reported a higher rate of complications in the lymphadenectomy groups[17, 18]. Moreover, it is well admitted that lymphadenectomy increases intra operative complication rate, with increased vascular injury rate and requires blood transfusion more frequently[31]. In the ASTEC study, the risk of developing short-term major surgical complications was low in both groups but more women in the lymphadenectomy group developed specific complications of: ileus, deep-vein thrombosis, lymphocyst and major wound dehiscence.

Concerning the extent of lymphadenectomy, contradictory results have been published about the impact of para-aortic lymphadenectomy on the surgical morbidity or radiation-related complications in comparison with patients undergoing pelvic lymphadenectomy only. Some

published that para-aortic lymphadenectomy does not contribute to increased complications[80] while others reported that para-aortic lymphadenectomy increases both blood loss and time of surgery[19, 80]. At the contrary, the laparoscopic route has been related to a lower blood loss and lower rate of surgical complications[81].

Lymphedema remains the main late complication associated with lymphadenectomy. To compare the quality of life (QoL) of women with lower limb lymphedema (LLL), to women with lower limb swelling (LLS), and to women without LLL or LLS following treatment for EC, Rowlands et al. sent a follow-up questionnaire 3-5 years after EC diagnosis. The 639 women who responded were categorized as: Women with LLL (n=68), women with LLS (n=177) and women without LLL or LLS (n=394). Although LLL was associated with reductions in physical QoL, LLS was related to reductions in both physical and mental QoL.

The risk for lymphedema is correlated to the number of LN removed[82]. It has recently been reported that resection of more than 31 LNs and removal of CINDEIN were significantly related to the occurrence of postoperative lower-extremity lymphedema in EC[32]. Abu-Rustum et al. suggested that removal of CINDEIN is likely to be a factor contributing to the risk of postoperative lower extremity lymphedema[82]. Hareyama et al. recently reported that preservation of CINDEIN could reduce or prevent the incidence of lower extremity lymphedema after systematic lymphadenectomy for patients with gynecologic malignancies[33].

## DECISION FOR ADJUVANT TREATMENT BASED ON LYMPHADENECTOMY

Some authors advocate a therapeutic benefit of lymphadenectomy in early EC to tailor adjuvant therapy in high risk patients[83-85]. However, as previously detailed, LN metastasis is usually found in patients with uterine risk factors that could justify adjuvant treatment in EC irrespectively to the LN status. Indeed, patients with high-risk early stage EC treated with adjuvant chemoradiotherapy have a lower rate of recurrence compared to those not receiving such therapy[86].

On the one hand, it seems logical to avoid a treatment characterised by morbidity and costs without survival benefit (ie, radiotherapy) by choosing another procedure (ie, lymphadenectomy) to select patients who will benefit from radiotherapy on a survival point of view. On the other hand, we believe important to remind that none of the five randomized studies evaluating adjuvant radiotherapy in stage I EC has shown improved survival in patients treated with adjuvant radiotherapy[87-91].

The benefit of chemotherapy in early stage EC has been poorly investigated[92, 93]. In Randall et al. trial comparing whole-abdominal irradiation and doxorubicin-cisplatin chemotherapy in women with stage III or IV EC having a maximum of 2 cm of postoperative residual disease, chemotherapy significantly improved survival compared with whole-abdominal irradiation[94]. Since approximately half of patients where stage III because of metastatic LN (FIGO 1988 Stage IIIC), these results constitute a strong argument for adequate systematic surgical staging (including LN assessment) and justify to deliver chemotherapy in patients with metastatic LN[20, 93, 95]. This study is pivotal since it showed for the first time that EC is a chemosensitive disease.

In Hogberg et al. study randomizing patients with stage I-III high risk EC receiving adjuvant radiotherapy with or without sequential chemotherapy, in patients not undergoing

lymphadenectomy, chemotherapy resulted in a gain of survival to the same extent than those who underwent lymphadenectomy[96]. Unfortunately, because only 26% of patients underwent pelvic lymphadenectomy (i.e. LN assessment), it was not possible to compare the impact of chemotherapy according to the LN status and we can not exclude that chemotherapy is beneficial in patients with positives LN only. It is possible that LN negative patients do not benefit from chemotherapy and in such patients we could safely avoid chemotherapy administration. The ongoing EORCT 55012 trial aims to answer this question by comparing survival in patients with stage I grade 3 endometrioid EC, stage I and II type 2 EC or stage II endometrioid EC and without metastatic LN after randomization for adjuvant chemotherapy. If survival in patients receiving adjuvant chemotherapy is better in patients receiving chemotherapy, LN assessment should not remain a standard procedure for LN negative intermediate and high risk EC since benefit of adjuvant chemotherapy will be proven irrespective for LN status. At the contrary, if no benefit is observed in patients receiving adjuvant chemotherapy, LN assessment will permit to avoid unnecessary chemotherapy side effects in LN negative patients.

## SENTINEL LYMPH NODE (SLN) BIOPSY

The SLN is defined as the first LN in the lymphatic system that drains a tumor site. If the SN is not metastatic, all other LNs should also be disease-free. The SLN procedure has been suggested to reliably predict the metastatic status of the regional LNs in early stage EC. Two main outcomes should be assessed when evaluating the interest of the SLN biopsy procedure. First, could be it a trade-off between systematic lymphadenectomy and no dissection at all? From the largest study evaluating the value of SLN biopsy[97] in EC, we can conclude that this strategy is not appropriate in high risk disease. In this trial, all three false-negative patients had type 2 EC. Concerning low and intermediate risk, in a recent meta-analysis, 35 studies with enough information for false negative rate evaluation and 51 studies (including the sub-groups of individual studies) for detection rate evaluation (2,071 patients overall) were included. Pooled detection rate was 78% and pooled sensitivity was 89%[98]. Cervical injection, as well as using both blue dye and radiotracer, resulted in higher detection rate and sensitivity. Using both blue dye and radiotracer and cervical injection of the mapping material could improve the sensitivity and detection rate of this technique. Larger studies are still needed to evaluate the false negative rate and the factors influencing the sensitivity before considering this method safe.

Second, the SLN biopsy procedure permits to identify “low-volume LN metastases”[99] because pathologic ultrastaging is the only method allowing detection of such LN disease. The frequency of such “low-volume, ultrastage-detected LN metastases” has been reported to be around 5% and interestingly, in such patients, the rate of micrometastases and isolated tumor cells does not seem to be correlated with myometrial invasion[99] and primary tumoral aggressiveness[100]. However, the oncologic significance of “low volume LN metastases” has not been reported yet.

**Practice points**

- Lymph node metastasis constitutes a major independent prognostic factors of endometrial cancer
- Stages IIIC1(pelvic lymph node invasion) and IIIC2 (para-aortic lymph node invasion) have very different prognosis
- A few percent of patients with negative pelvic lymph node have para-aortic invasion
- For optimal LN metastatic resection in endometrial cancer, resection of deep inguinal nodes is not recommended, whereas para-aortic lymphadenectomy should be extended up to the level of renal veins.
- MRI and successful sentinel node biopsy are the most preoperative accurate tests for identifying LN metastasis.
- Result of positive 18F-FDG PET in the LN is reliable for the diagnosis of metastasis.
- Various scores mainly based on primary tumoral characteristics are available to predict LN metastasis. Most of them have not been externally validated but can permit to avoid lymphadenectomy in half of patients.
- LVSI should be considered to be an independent risk factor for LN metastasis.
- In low risk group patients, lymphadenectomy has no impact on survival.
- In intermediate and high risk group patients, the therapeutic impact of lymphadenectomy is not proven. But, the procedure can identify patients that may benefit from adjuvant chemotherapy
- Lymphadenectomy is associated with a higher rate of complications. The risk for lymphedema is correlated to the number of LN removed.

**Research agenda**

- Evaluation of new imaging techniques to identify metastatic LN in patients with EC (such as fused PET/MRI)
- Comparison of the various scores to predict metastatic LN
- Identification of biomarkers able to predict metastatic LN pre operatively
- Identification of a subgroup of patients who will benefit of lymphadenectomy in terms of survival
- Technique of sentinel lymph node procedure
- Identification of patients who will benefit from sentinel lymph node biopsy
- Cost effectiveness analysis for lymphadenectomy practice in EC
- The value of adjuvant chemotherapy in node negative disease

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**Table 1.** Diagnostic performance of 18-F-FDG PET imaging for Lymph node staging of endometrial cancer.

| | Sensitivity,% | Specificity,% | LR+ | LR- | DOR |
|---|---|---|---|---|---|
| LN overall | 72 (64-80) | 93 (91-95) | 8.4 (5.9-11.8) | 0.4 (0.2-0.5) | 27.7 (15.8-48.6) |
| Pelvic LN | 61 (48-73) | 97 (95-99) | 15.4 (8.6-27.5) | 0.4 (0.2-0.9) | 42.0 (18.8-93.6) |
| PA LN | 87 (66-97) | 99 (97-100) | 46.6 (18.4-117.9) | 0.1 (0.05-0.4) | 309 (70.6-1352) |

LR+: Positive likelihood ratio

LR-: Negative likelihood ratio

DOR: Diagnostic odds ratio

**Table 2.** Available scores to predict lymph node metastatic in patients with endometrial cancer

| Score | Components | Evaluated | Externaly validated | Low risk |
|---|---|---|---|---|
| **Kang et al. 2012**[50] | CA125, MRI locoregional extension (myometrial invasion, LN enlargement, and extension beyond uterine corpus) | Pre operatively | Yes | 43%<br>1.4% |
| **Lee et al. 2010**[47] | CA125, grade, MRI locoregional extension (disease extent and myometrial invasion) | Pre operatively | No | 57%<br>0% |
| **Kamura et al. 1999**[46] | Pathological local extension (tumor diameter and myometrial invasion) | Post operatively | No | Not reported |
| **Todo et al. 2007**[48, 51] | CA125, tumor grade/histology, MRI local extension (volume index) | Pre operatively | Yes | 54%<br>3% |
| **Luomaranta et al. 2013**[49] | Biochemical factors (leukocytosis, thrombocytosis and CA125 level) and preoperative tumor characteristics | Pre operatively | No | Not reported |
| **Bendifallah et al. 2012**[45, 52] | Pathological hysterectomy characteristics (subtype; grade and myometrial and cervical invasion), age and race | Pre operatively and Post operatively | Yes | 54%<br>0% |
| **Milam et al. 2012**[53] | Uterine pathology characteristics (myometrial invasion, tumor size, and differentiation) | Post operatively | No | 40%<br>0.8% |